



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,647	07/31/2006	Rosanne M Crooke	ISPH-0595USA	5096
72984	7590	07/31/2008	EXAMINER	
JONES DAY for Isis Pharmaceuticals, Inc. 222 East 41st Street New York, NY 10017-6702			BOWMAN, AMY HUDSON	
			ART UNIT	PAPER NUMBER
			1635	
			MAIL DATE	DELIVERY MODE
			07/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/559,647	Applicant(s) CROOKE ET AL.	
	Examiner AMY BOWMAN	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,6,8-11,17,50 and 52-67 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,6,8-11,17,50 and 52-67 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 2/15/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/15/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 6, 8-11, 17, 50 and 52-67 are pending in the application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/15/08 has been entered.

Applicant's arguments and/or amendments filed 2/15/08, with respect to the rejection(s) of claim(s) under 35 USC 112, 1st paragraph; 35 USC 102; and 35 USC have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made as explained below.

Priority

As explained in the office actions mailed on 5/14/07 and 11/15/07, applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application No. 60/475,402 and Application No. 10/684,440, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The applications do not teach antisense compounds that are targeted specifically to the range of nucleotides "12380-13493" of instant SEQ ID NO: 4 and do not teach the sequence of instant SEQ ID NO: 87.

Therefore, the instant claims are accorded an effective filing date of 6/2/04, the filing date of PCT/US04/14540.

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 17, 54 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Scanu et al. (WO 97/17371).

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94%, 95%, or is 100% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4, wherein the compound is a single stranded antisense oligonucleotide.

Scanu et al. teach a primer that is an oligonucleotide in the antisense direction and is single stranded, meeting the instant limitation of a single stranded antisense oligonucleotide. The antisense oligonucleotide sequence of Scanu et al. is 22 nucleotides in length and is 100% complementary to nucleotides 12830-12851 of instant SEQ ID NO: 4 (see SEQ ID NO: 2 on page 115 of Scanu et al., as well as search result # 1 in the file labeled "20070502_094835_us-10-559-647-4_copy_12380-13493.sl.rng" in SCORE, wherein SEQ ID NO: 2 of Scanu et al. is 100% complementary to nucleotides 451-472 within the region of nucleotides 12380-13493, wherein nucleotide 12380 is considered nucleotide position 1 in the search results).

Although Scanu et al. is silent as to the oligonucleotide being targeted to a nucleic acid molecule encoding apolipoprotein (a), the oligonucleotide is necessarily targeted to such a sequence as it meets the instant structural limitations of being fully complementary to the instantly recited region of instant SEQ ID NO: 4. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property.

Therefore, the instant claims are anticipated by Scanu et al.

Claims 1, 3, 6, 8-11, 17, and 54-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Crooke et al. (WO 03/014307 A3).

It is noted that this reference is of record and was cited on the IDS filed by applicant on 4/11/07.

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94%, 95%, or is 100% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4, wherein the compound is a single stranded antisense oligonucleotide. The claims are directed to modifications, configurations thereof, length requirements, and stringency requirements between the antisense compound and the target nucleic acid.

Crooke et al. teach antisense oligonucleotides 20 nucleotides in length that are 100% complementary to nucleotides 12461-12480, nucleotides 12699-12718, and nucleotides 13354-13373 (see SEQ ID NOs: 32-34, respectively on page 87 of Crooke

Art Unit: 1635

et al.). The oligonucleotides of Crooke et al. are chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap that target human apolipoprotein (a) (see Table 1 on page 87). Not only does Crooke et al. teach the specific gapmer configuration, but also teaches 5'-methylcytosine and bicyclic modifications.

Therefore, the instant claims are anticipated by Crooke et al. It is noted that WO 03/014307 A3 has the same inventors as the instant application. However, the reference was published more than one year before the priority date of the instant claims and is therefore prior art under 35 USC 102(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 6, 8-11, 17, and 54-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruoy et al. (WO 99/35241), in view of Stinchcomb et al. (WO 96/09392), Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109), Baracchini et al. (US 5,801,154), and Ramasamy (US 6,525,191 B1).

It is noted that Baracchini et al. and Ruoy et al. are of record and cited on the PTO-892 form mailed on 5/14/07.

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94%, 95%, or is 100% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4, wherein the compound is a single stranded antisense oligonucleotide. The claims are directed to modifications, configurations thereof, length requirements, and stringency requirements between the antisense compound and the target nucleic acid.

Ruoy et al. teach antisense nucleic acids that are capable of specifically hybridizing with a nucleic acid encoding apolipoprotein (a) and down regulating gene expression (see page 23, first full paragraph). Ruoy et al. teach that preferably the antisense sequence is at least 20 nucleobases in length and that the antisense oligonucleotides can be modified to improve their stability and selectivity.

Ruoy et al. do not teach antisense oligonucleotides that are at least 90% complementary to nucleotides 12380-13493 of apolipoprotein (a) SEQ ID NO: 4 or the specific modifications that are instantly claimed.

Stinchcomb et al. teach an antisense compound, more specifically a ribozyme that is targeted to a sequence in human apo(a) that is 100% identical to nucleotides 12974-12988 of instant SEQ ID NO: 4 (see Table II on page 18 of Stinchcomb et al., ribozyme target sites of nucleotide positions 12453, 12481, 12592, 12650, 12974, 12976, 13119, 13226, and 13228). Stinchcomb et al. teach that incorporating chemical modifications into ribozymes prevents their degradation by serum ribonucleases (see page 12).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity and teach compositions comprising the oligonucleotides with a pharmaceutical carrier. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The

Art Unit: 1635

gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides and specifically teach 2'-MOE modifications. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

Baracchini et al. teach antisense oligonucleotides with modifications such as phosphorothioates, 2'-O-methoxyethyl sugar moieties, and 5-methylcytosine nucleobase modifications (columns 6 and 7). Additionally, Baracchini et al. teach chimeric oligonucleotides containing two or more chemically distinct regions (column 8). Baracchini et al. teach antisense oligonucleotides that it is preferable to target the coding region and for antisense oligonucleotides to be 8-30 nucleobases in length. Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al. teach that it is preferable for antisense oligonucleotides to be 100% complementary to the selected target.

Baracchini et al. teach that typically chimeric oligonucleotides are "gapped" oligonucleotides (or "gapmers") in which a region of deoxynucleotides (the "gap"), preferably containing at least four contiguous deoxynucleotides, is flanked by regions of modified nucleotides, preferably 2'-sugar modified nucleotides. In a preferred embodiment, the flanking regions (or "wings") contain 2'-alkoxy or 2'-alkoxyalkoxy

Art Unit: 1635

modifications, more preferably 2'-methoxyethoxy. In preferred embodiments the backbone may be phosphorothioate throughout or may be phosphodiester in the "wings" and phosphorothioate in the "gap". In other preferred embodiments, chimeric oligonucleotides may be "winged" oligonucleotides (or "wingmers" or hemichimeras) in which there is a deoxy "gap", preferably at least 4 contiguous deoxynucleotides, flanked on either the 5' or the 3' side by a region of modified nucleotides. Again, the flanking region (or "wing") preferably contains 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy and the backbone may be phosphorothioate throughout or may be phosphodiester in the "wing" and phosphorothioate in the "gap". Other configurations of chimeric oligonucleotide are also comprehended by this invention. These may involve other modifications of the sugar, base or backbone, preferably in the oligonucleotide wing(s).

Ramasamy teaches bicyclic nucleic acid sugar moieties for antisense oligonucleotides and teaches that such moieties may have superior inhibitory properties.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to make an antisense oligonucleotide to apolipoprotein (a) as taught by Ruoy et al. targeted to the specific target regions of Stinchcomb et al. with the modifications taught by Baracchini et al., Olie et al. and Ramasamy.

One would have been motivated to target the specific portions of the coding region of apolipoprotein (a) that are targeted with the ribozymes of Stinchcomb et al. with an antisense oligonucleotide because both antisense oligonucleotides and

Art Unit: 1635

ribozymes rely upon accessibility of the target region and are sterically inhibited by secondary structure. Since the regions of Stinchcomb et al. were determined to be accessible to ribozymes, as evidenced by Stinchcomb et al., one would be motivated to target the same region with an antisense oligonucleotide and expect for the region to be accessible. One would certainly expect for an apo (a) antisense oligonucleotide to result in inhibition of apo (a) expression when targeted to a specific region of apo (a) that is accessible to a ribozyme.

One would have been motivated to incorporate a chimeric configuration, 2'-O-methoxyethyl sugar moieties, phosphorothioate linkages, or 5-methylcytosine modifications into the antisense oligonucleotides of Ruoy et al. because Baracchini et al. teaches each of these elements and teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Incorporation of chemical modifications into gapmer configurations is also taught by Olie et al. as being optimal. One would have been motivated to incorporate a bicyclic sugar moiety because Ramasamy teaches that such moieties may have superior inhibitory properties.

One would have a reasonable expectation of success for each of the instant modifications to benefit the antisense oligonucleotides of Ruoy et al. because the chemistry was well known, as demonstrated by Baracchini et al., Olie et al., and Ramasamy. Ruoy et al. teaches that it is beneficial to modify antisense

Art Unit: 1635

oligonucleotides, whereas Baracchini et al., Olie et al. and Ramasamy teach specific chemical modifications for the same benefits.

One would have a reasonable expectation of success in generating an active antisense oligonucleotide when targeting the antisense oligonucleotides of Ruoy et al. to the specific regions of the apo (a) coding region that are taught to be target regions for ribozymes, as evidenced by Stinchcomb et al. because one would expect for the region to be accessible to antisense oligonucleotides based upon accessibility to ribozymes, which have even additional hindrances based upon the complex structure of the ribozyme in combination with target accessibility.

Therefore, the invention of the above claims would have been obvious, as a whole, at the time the instant invention was made.

Claims 1, 3, 6, 8-11, 50 and 52-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Stinchcomb et al. (WO 96/09392), Tuschl et al. (The siRNA user guide, pages 1, 3 and 5, 8/26/01 (on-line), retrieved 1/31/02, Max Planck Institute for Biophysical Chemistry, <http://www.mpibpc.gwdg.de/abteilungen/100/105/siRNAuserguide.pdf>), Holen et al. (Nucleic Acids Research, 2002, Vol. 30, No. 8, pages 1757-1766), Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109), Baracchini et al. (US 5,801,154), and Ramasamy (US 6,525,191 B1).

It is noted that Baracchini et al. and Ruoy et al. are of record and cited on the PTO-892 form mailed on 5/14/07.

The instant claims are directed to an antisense compound 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein(a), wherein said compound is at least 94%, 95%, or is 100% complementary to nucleotides 12380-13493 as set forth in SEQ ID NO: 4, wherein the compound is a single stranded antisense oligonucleotide. The claims are directed to modifications, configurations thereof, length requirements, and stringency requirements between the antisense compound and the target nucleic acid.

It is noted that the instant rejection is strictly directed to double-stranded compounds. Recitation of single-strandedness in the claims, for example, would obviate this rejection.

Elbashir et al. teach that duplexes of 21-23 nucleotide RNAs are the sequence-specific mediators of RNA interference. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs are the most efficient triggers of sequence-specific mRNA degradation (see abstract). Elbashir et al. teach duplexes with overhangs as well as blunt ended duplexes that resulted in RNAi activity (see Figure 1, for example). Elbashir et al. teach duplexes wherein each strand is 19 nucleotides in length (see Figure 2, for example). Elbashir et al. teach that these elements provide a rational basis for the design of siRNAs in future gene targeting experiments (see abstract).

Elbashir et al. teach siRNAs wherein each strand is 20 nucleobases in length (see Fig. 2, for example). Elbashir et al. teaches siRNA molecules comprising 2'-deoxy

Art Unit: 1635

modifications and unmodified RNA nucleotides that resulted in RNAi activity. Since the siRNA molecules have more than one chemically distinct region, the siRNA molecules meet the instant limitation of being chimeric. Elbashir et al. teach that incorporation of 2'-deoxy substitutions did not affect RNAi, but help to reduce the cost of RNA synthesis and may enhance RNase resistance of the siRNA duplexes (see page 6885, column 1).

Elbashir et al. does not teach siRNAs directed to apolipoprotein (a) or the specific region of apo (a), as instantly recited. Elbashir et al. does not teach 2'-O-methoxyethyl, phosphorothioate, 5-methylcytosine, or bicyclic modifications, or combinations thereof.

Stinchcomb et al. teach an antisense compound, more specifically a ribozyme that is targeted to a sequence in human apo(a) that is 100% identical to nucleotides 12974-12988 of instant SEQ ID NO: 4 (see Table II on page 18 of Stinchcomb et al., ribozyme target sites of nucleotide positions 12453, 12481, 12592, 12650, 12974, 12976, 13119, 13226, and 13228). Stinchcomb et al. teach that incorporating chemical modifications into ribozymes prevents their degradation by serum ribonucleases (see page 12).

Tuschl et al. teach selection guidelines for siRNA duplexes based upon a target mRNA sequence. Tuschl et al. teach that the most efficient silencing was obtained with siRNA duplexes composed of 21-nt sense and antisense strands, paired in a manner to have a 2-nt 3' overhang. Tuschl et al. teach selection of target regions, guidelines in selecting preferred siRNAs directed to that target, and blast search comparison of the resultant siRNA molecules to ensure specificity.

Holen et al. teaches synthesis of several siRNAs against different sites on the same target mRNA, wherein the siRNAs demonstrated striking differences in silencing efficiency (see abstract). Holen et al. walked siRNAs in three nucleotide increments to determine the effect on silencing efficiency (see Figure 2), thus demonstrating that siRNA activity is routinely optimized by shifting target position across the mRNA sequence. The siRNAs resulted in varying activity, although each did result in silencing.

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity and teach compositions comprising the oligonucleotides with a pharmaceutical carrier. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides and specifically teach 2'-MOE modifications. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

Baracchini et al. teach antisense oligonucleotides with modifications such as phosphorothioates, 2'-O-methoxyethyl sugar moieties, and 5-methylcytosine nucleobase modifications (columns 6 and 7). Additionally, Baracchini et al. teach

Art Unit: 1635

chimeric oligonucleotides containing two or more chemically distinct regions (column 8).

Baracchini et al. teach antisense oligonucleotides that it is preferable to target the coding region and for antisense oligonucleotides to be 8-30 nucleobases in length.

Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al. teach that it is preferable for antisense oligonucleotides to be 100% complementary to the selected target.

Baracchini et al. teach that typically chimeric oligonucleotides are "gapped" oligonucleotides (or "gapmers") in which a region of deoxynucleotides (the "gap"), preferably containing at least four contiguous deoxynucleotides, is flanked by regions of modified nucleotides, preferably 2'-sugar modified nucleotides. In a preferred embodiment, the flanking regions (or "wings") contain 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy. In preferred embodiments the backbone may be phosphorothioate throughout or may be phosphodiester in the "wings" and phosphorothioate in the "gap". In other preferred embodiments, chimeric oligonucleotides may be "winged" oligonucleotides (or "wingmers" or hemichimeras) in which there is a deoxy "gap", preferably at least 4 contiguous deoxynucleotides, flanked on either the 5' or the 3' side by a region of modified nucleotides. Again, the flanking region (or "wing") preferably contains 2'-alkoxy or 2'alkoxyalkoxy modifications, more preferably 2'-methoxyethoxy and the backbone may be phosphorothioate throughout or may be phosphodiester in the "wing" and phosphorothioate in the "gap". Other

Art Unit: 1635

configurations of chimeric oligonucleotide are also comprehended by this invention.

These may involve other modifications of the sugar, base or backbone, preferably in the oligonucleotide wing(s).

Ramasamy teaches bicyclic nucleic acid sugar moieties for antisense oligonucleotides and teaches that such moieties may have superior inhibitory properties.

It would have been obvious to design a siRNA, as taught by Elbashir et al., that is targeted to nucleotides 12380-13493 of instant SEQ ID NO: 4 and meeting the instant stringency requirements. It would have been obvious to incorporate the instant modifications and combinations/configurations of the modifications into the siRNA of Elbashir et al.

It would have been prima facie obvious to perform routine optimization to walk the known target sequence to design any given siRNA against the sequence in view of the guidelines taught by Elbashir et al., Tuschl et al., and Holen et al., as noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular element used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. It was known in the art that the activity of a siRNA duplex can be optimized by shifting the target

sequence, as evidenced by Holen et al. and design guidelines were known in the art to determine optimal siRNAs, as evidenced by Elbashir et al. and Tuschl et al.

Since it was known to target the instant region of instant SEQ ID NO: 4 with ribozymes, as evidenced by Stinchcomb et al., one would have been motivated to inhibit the expression of apo (a) with a siRNA as well, as it was known that siRNAs can easily knock down the expression of mammalian genes, as evidenced by Tuschl et al. One would have been motivated to utilize an siRNA because Tuschl et al. teaches that one would be amazed how easy it is to knock-down a mammalian gene via following the guidelines taught by Tuschl et al. Therefore, it would simply be a matter of design choice to design a siRNA rather than a ribozyme, wherein the siRNA is directed to the same region that had been deemed accessible by targeting a ribozyme to, as evidenced by Stinchcomb et al.

Furthermore, one would have been motivated to design the siRNA to have the structural characteristics set forth by Elbashir et al. because Elbashir et al. teaches guidelines and sets forth that the results provide a rational basis for the design of siRNAs.

With regards specifically to the siRNA being targeted to the instant region of SEQ ID NO: 4 and with the instant stringencies, siRNAs of this genus are within the genus that would result from routine optimization of the guidelines/testing set forth by Elbashir et al., Tuschl et al. and Holen et al. One would have been motivated to design siRNAs specific for human endothelial lipase via utilizing the rules of Tuschl et al. and walking the target sequence as evidenced by Holen et al. Applicant has not demonstrated any

unexpected result for the instant genus of siRNAs, wherein such sequences would have resulted from the rational design of siRNAs to endothelial lipase following the published guidance of Tuschl et al. and Holen et al.

In view of the availability of targeting guidelines, as taught by Tuschl et al., and the known optimization of siRNA duplexes via walking the target sequence, as evidenced by Holen et al., one of skill would have been able to envision every siRNA directed to the instant target apo (a) sequence. Although the relative activities would need to be experimentally determined, the majority of such siRNAs designed via the rules established in the art have some level of RNA interference activity.

As set forth in MPEP 2144.08, a species is obvious in view of the genus where one of skill would be able to immediately envision each species. Although the instant genus is large, one of skill would have been able to immediately envision each species of siRNA molecules targeted to apo (a) in view of the guidelines set forth by Tuschl et al. and readily available design algorithms. It would have been obvious to one of skill to select any given siRNA targeted to apo(a) based on the guidelines of Tuschl et al. and the optimization of Holen et al.

One would have been motivated to incorporate each of the instantly recited modifications because each of the modifications were known in the art to enhance the cellular uptake, enhance affinity for the nucleic acid target and increase stability of antisense oligonucleotides in the presence of nucleases, as evidenced by the combined teachings of Baracchini et al., Olie et al., and Ramasamy. Since ribozymes, antisense oligonucleotides and siRNA molecules are each sequence specific inhibitory nucleic

Art Unit: 1635

acid molecules that face delivery challenges in the cell, one would have been motivated to incorporate the modifications of Baracchini et al., Olie et al. and Ramasamy into the siRNA of Elbashir et al., which is further supported by the fact that Elbashir et al. does incorporate modifications and teaches that modifications reduce cost and may enhance siRNA stability in the presence of RNases. Therefore, one would have certainly been motivated to try other modifications that were known to benefit antisense oligonucleotides in the siRNAs of Elbashir et al in order to optimize the activity therein.

Furthermore, one would have been motivated to incorporate combinations of the modifications as well as gapmer configurations, as Olie et al. teaches that such configurations resulted in increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity and to deliver nucleic acids in a composition with a carrier.

Finally, one of skill in the art would have had a reasonable expectation of success at generating a siRNA duplex that anticipates the instant genus because Stinchcomb et al. offers motivation to design inhibitory nucleic acids to the instant region based upon the ribozyme target regions of Stinchcomb et al., Elbashir et al. and Tuschl et al. teach design guidelines for siRNA molecules against any given mammalian target; and Holen et al. teaches walking a target sequence to optimize activity of the siRNA.

Art Unit: 1635

Therefore, one would expect for the guidelines established by Elbashir et al., Tuschl et al. and Holen et al. to result in molecules that would fall within the instant genus.

Furthermore, Elbashir et al. teaches rational design guidelines for siRNA molecules including lengths and chemical modifications.

Although the genus of possible siRNA molecules that would be produced by the guidelines of the prior art is very large, it is within the realm of routine optimization to determine optimal siRNA molecules from the genus, as evidenced by Tuschl et al. and Holen et al. The genus of siRNA molecules directed to the instant target sequence is described in the art because the target sequence was known, as evidenced by Stinchcomb et al. and guidelines were established for designing siRNAs to a given target, as evidenced by Tuschl et al. Therefore, one of skill in the art had the tools to aid and predict which siRNA molecules will have the required function, and can readily make and test the siRNAs for resultant RNAi activity, consistent with the published Written Description Guidelines (i.e. Example 12).

One would have had a reasonable expectation that the modifications and configurations thereof would benefit in the stability and delivery of the siRNA molecules of Elbashir et al. in view of the teachings of Olie et al., Ramasamy and Baracchini et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

It is noted that in the office action mailed on 11/15/07, claims 52 and 53 were objected to as being dependent upon a rejected base claim, but were set forth as allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The potential allowability of the subject matter is withdrawn in view of the rejections set forth above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1635

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AMY BOWMAN/
Examiner, Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635